DB Name	Query	Hit Count	Set Name
USPT	l1 and l13	52	L32
USPT	l29 and l13	16	L31
USPT	l1 and l29	0	L30
USPT	expand$4 same l28	74	L29
USPT	hydroxypropylcellulose or hydroxy propyl cellulose or hydroxypropyl cellulose	14473	L28
USPT	l26 and l24	2	L27
USPT	dioctyl sodium sulfosuccinate or dss or stool softener	3385	L26
USPT	l1 and l24	0	L25
USPT	expand$4 same l10	63	L24
USPT	expand$4 same polymer	10237	L23
USPT	l5 and l10	0	L22
USPT	l5 same l10	0	L21
USPT	l5 same polymer	0	L20
USPT	l5 and polymer$1	1	L19
USPT	l15 same l16	3078	L18
USPT	l16.ti. l16.ab.	0	L17
USPT	block$4 or obstruct$4	1002487	L16
USPT	swell$4	60392	L15
USPT	l12 and l13	13	L14
USPT	sustained release	12822	L13
USPT	l1 and l10	38	L12
USPT	l5 and l10	0	L11
USPT	hydroxyethylcellulose or hydroxy ethyl cellulose or hydroxyethyl cellulose	20946	L10
USPT	l1 and l2	0	L9
USPT	l1 and l7	0	L8
USPT	l2.ti. or l2.ab.	10	L7
USPT	l5 and l2	0	L6
USPT	l1.ti. or l1.ab.	1	L5
USPT	l1 near l2	0	L4
USPT	l1 same l2	0	L3
USPT	(fed or postprandial or digestive) near1 mode	471	L2
USPT	docusate	173	L1

L32: Entry 7 of 52 File: USPT Aug 22, 2000

DOCUMENT-IDENTIFIER: US 6106865 A
TITLE: Pharmaceutical excipient having improved compressibility

BSPR:
The present invention is also directed to a compressed solid dosage form comprising an active ingredient(s) and the novel excipient described herein, wherein the active agent and excipient have been directly compressed into the solid dosage form or have been subjected to a wet granulation procedure and thereafter compressed into the solid dosage form. The compressed solid dosage form provides a suitable release dissolution profile of the active ingredient(s) when exposed to aqueous solutions during in-vitro dissolution testing, and provides a release of drug in an environment of use which is considered bioavailable. In one embodiment of the invention, the dissolution profile of the solid dosage form is suitable for immediate release of the active agent. In further embodiments of the invention, the dissolution profile of the solid dosage form is modified to provide a controlled or sustained release dissolution profile.

DRPR:
FIG. 7 graphically shows a comparison of the tensile strength of tablets prepared in accordance with the invention to contain microcrystalline cellulose coprocessed with sodium lauryl sulfate, tablets containing microcrystalline cellulose coprocessed with docusate sodium and prior art tablets prepared to contain only unmodified microcrystalline cellulose.

DEPR:
Alternative anionic surfactants include docusate salts such as the sodium salt thereof. Other suitable anionic surfactants include, without limitation, alkyl carboxylates, acyl lactylates, alkyl ether carboxylates, N-acyl sarcosinates, polyvalent alkyl carbonates, N-acyl glutamates, fatty acid, polypeptide condensates and sulfuric acid esters.

DEPR:
In these examples, the coprocessing method described in Example 23A was repeated except that docusate sodium (Spectrum Chemical) was used as the coprocessing agent).

DEPR:
Referring now to FIG. 7, it can be seen that coprocessing microcrystalline cellulose with docusate sodium also affords the retention of microcrystalline cellulose compressibility.

DEPC:
Docusate Sodium

DETL:

Example	Docusate Sodium (wt %)		
31	0.25	32	0.50

L32: Entry 18 of 52 File: USPT Jan 12, 1999

DOCUMENT-IDENTIFIER: US 5858412 A
TITLE: Sustained release formulations utilizing pharmaceutical excipient having improved compressibility with modified microcrystalline

ABPL:
Sustained release formulations include an augmented microcrystalline cellulose, an active agent, and a sustained release carrier and methods for making same are disclosed.

BSPR:
The present invention relates to sustained-release solid dosage forms such as, e.g. tablets or capsules, which include one or more active ingredients and one or more novel excipients having desirable characteristics suitable for use in wet-granulation processes.

BSPR:
In order to prepare a compressed sustained-release solid dosage form containing one or more active ingredients (such as drugs), it is necessary that the material to be compressed into the dosage form possess certain physical characteristics which lend themselves to processing in such a manner. Among other things, the material to be compressed must be free-flowing, must be lubricated, and, importantly, must possess sufficient cohesiveness to insure that the solid dosage form remains intact after compression.

BSPR:
Due to the loss of compressibility, microcrystalline cellulose has typically only been used in immediate release formulations prepared via direct compression. Although the properties of microcrystalline cellulose are well-suited for the preparation of immediate release dosage forms, due to the problems associated with use of microcrystalline cellulose in wet-granulation, it is not well-adapted for use in sustained-release dosage forms which are typically prepared by wet-granulation.

BSPR:
There still remains a need in the industry for sustained-release dosage forms utilizing excipients possessing excellent compressibility whether utilized in a direct compression or wet granulation procedure.

BSPR:
It is an object of the invention to provide sustained-release formulations which include an excipient which is useful in a variety of applications, and which may be prepared via wet-granulation or direct compression methods.

BSPR:
It is further an object of the invention to provide sustained-release formulations which include an excipient useful in direct compression methods which has improved compressibility relative to microcrystalline cellulose.

BSPR:
It is further an object of the invention to provide sustained-release formulations which include an excipient which is useful in wet granulation methods which has improved compressibility relative to microcrystalline cellulose.

BSPR:
It is further an object of the invention to provide methods of preparing sustained-release formulations utilizing wet-granulation techniques.

BSPR:
In view of the above objects and others, the present invention is directed to sustained-release formulations comprising an active ingredient, an augmented microcrystalline cellulose which possesses excellent compressibility whether utilized in a direct compression or wet granulation procedure, and a sustained-release carrier. The sustained-release is, e.g. a pharmaceutically acceptable hydrophobic and/or hydrophilic material which can be processed together with the active ingredient and augmented microcrystalline cellulose into a matrix, or can be applied to a core or substrate comprising the active ingredient and the augmented microcrystalline cellulose.

BSPR:
The present invention to is also directed to processes of preparing sustained-release formulations utilizing an augmented microcrystalline cellulose and a sustained-release carrier.

BSPR:
In another embodiment of the invention there is provided sustained-release formulations which include an immediate release core comprising an augmented microcrystalline cellulose and an effective amount of an active agent. The immediate release core is coated with an effective amount of a sustained-release carrier to promote sustained-release of the therapeutic agent. The core may be in the form of, e.g. a compressed tablet.

BSPR:
The invention further relates to a method of preparing a sustained-release formulation by wet granulating a sustained-release carrier, an augmented microcrystalline cellulose and an active agent to obtain a wet mass, drying the wet mass to obtain an agglomerated particulate, and dividing the agglomerated particulate into unit doses comprising a therapeutically effective amount of the active agent. The unit dose may then be, e.g. preferably compressed to form a tablet, or encapsulated in a hard gelatin capsule to make a desired sustained-release dosage form.

BSPR:
In another embodiment of the invention, there is provided a method of preparng a sustained-release dosage form by preparing an immediate release tablet core by wet-granulating an augmented microcrystalline cellulose together with an effective amount of a therapeutic agent and compressing the resultant mixture to form the immediate release core and coating the core with an effective amount of a sustained-release carrier to promote sustained-release of the therapeutic agent.

BSPR:
Alternative anionic surfactants include docusate salts such as the sodium salt thereof. Other suitable anionic surfactants include. without limitation, alkyl carboxylates, acyl lactylates, alkyl ether carboxylates, N-acyl sarcosinates, polyvalent alkyl carbonates, N-acyl glutamates, fatty acid, polypeptide condensates and sulfuric acid esters.

BSPR:
In one embodiment of the invention, the sustained-release carrier is incorporated in a sustained-release matrix to impart sustained-release of the active agent from the final formulation. The sustained release carrier may be hydrophobic or hydrophilic. Suitable materials which may be included in the sustained release carrier of the present invention include alkylcelluloses such as natural or synthetic celluloses derivatives (e.g. ethylcellulose), acrylic and methacrylic acid polymers and copolymers, zein, and mixtures thereof.

BSPR:

In another embodiment, suitable biocompatible, preferably biodegradable polymers can be utilized as the sustained release carrier. The biodegradable polymeric material may comprise a polylactide, a polyglycolide, a poly(lactide-co-glycolide), a polyanhydride, a polyorthoester, polycaprolactones, polyphosphazenes, polysaccharides, proteinaceous polymers, soluble derivatives of polysaccharides, soluble derivatives of proteinaceous polymers, polypeptides, polyesters, and polyorthoesters. The polysaccharides may be poly-1,4-glucans, e.g., starch glycogen, amylose, amylopectin, and mixtures thereof. The biodegradable hydrophilic or hydrophobic polymer may be a water-soluble derivative of a poly-1,4-glucan, including hydrolyzed arnylopectin, hydroxyalkyl derivatives of hydrolyzed amylopectin such as hydroxyethyl starch (HES), hydroxyethyl amylose, dialdehyde starch, and the like.

BSPR:
In yet other preferred embodiments, sustained-release of the active agent is accomplished via a sustained release carrier comprising a synthetic or naturally occurring gum. Examples of naturally occurring gums include, e.g., the heteropolysaccharides and homopolysaccharides. An especially preferred heteropolysaccharide is xanthan gum, which is a high molecular weight (>10.sup.6) heteropolysaccharide. Other preferred heteropolysaccharides include derivatives of xanthan gum, such as deacylated xanthan gum, the carboxymethyl ether, and the propylene glycol ester.

BSPR:
Water swellable polymers may be used in addition to or instead of gums to promote sustained-release of the active agent from the final formulation. Such water swellable polymers include cellulose ethers, carboxyvinyl polymer and the like.

BSPR:
The combination of xanthan gum with locust bean gum is an especially preferred gum combination. In certain embodiments, the controlled release properties of the sustained-release carrier are optimized when the ratio of heteropolysaccharide gum to galactomannan gum is from about 3:1 to about 1:3, and most preferably about 1:1. However, in this embodiment, the sustained release carrier of the invention may comprise from about 1% to about 99% by weight heteropolysaccharide gum and from about 99% to about 1% by weight homopolysaccharide gum.

BSPR:
Optionally, the sustained-release carrier includes a release modifying agent. A release modifying agent according to the invention includes any pharmaceutically acceptable substance which my alter, e.g. prolong or increase, the release rate of the active agent form the formulation upon exposure to an aqueous environment, e.g. gastric fluid or dissolution medium. Suitable release modifying agents which may be incorporated into the matrix formulations of the present invention include, e.g., monovalent or multivalent metal cations. Preferably, the salts are inorganic salts, including e.g., alkali metal and/or alkaline earth metal sulfates, chlorides, borates, bromides, citrates, acetates, lactates, etc. In particular, these salts include, e.g., calcium sulfate, sodium chloride, potassium sulfate, sodium carbonate, lithium chloride, tripotassium phosphate, sodium borate, potassium bromide, potassium fluoride, sodium bicarbonate, calcium chloride, magnesium chloride, sodium citrate, sodium acetate, calcium lactate, magnesium sulfate and sodium fluoride. Multivalent metal cations may also be utilized. In preferred embodiments, the release modifying agents are bivalent. Particularly preferred salts are calcium sulfate and sodium chloride.

BSPR:
In those embodiments including a release modifying agent any effective amount may be employed. Preferably, the release modifying agent is included in an amount ranging from about 1 to about 20% by weight of a sustained-release carrier comprising xanthan gum and locust bean gum.

BSPR:
The final sustained-release oral dosage form may contain from about 1 to about 99% (by weight) of sustained release carrier. Preferably, the weight percent of the sustained release carrier ranges from about 1 to about 80%.

BSPR:
In certain preferred embodiments of the present invention, the sustained release carrier is a pharmaceutically acceptable acrylic polymer, including but not limited to acrylic acid and methacrylic acid copolymers, methyl methacrylate, methyl methacrylate copolymers, ethoxyethyl methacrylates, cynaoethyl methacrylate, aminoalkyl methacrylate copolymer, poly(acrylic acid), poly(methacrylic acid), methacrylic acid alkylamine copolymer, poly(methyl methacrylate), poly(methacrylic acid)(anhydride), polymethacrylate, polyacrylamide, poly(methacrylic acid anhydride), and glycidyl methacrylate copolymers. In other embodiments, the sustained-release carrier may further include a relatively hydrophilic material, including but not limited to materials such as hydroxyalkylcelluloses such as hydroxypropylmethylcellulose and mixtures of the foregoing.

BSPR:
A pharmaceutically acceptable plasticizer may also optionally be included in the sustained-release carrier of the present invention. A non-limiting list of plasticizers includes include water insoluble plasticizers such as dibutyl sebacate, diethyl phthalate, triethyl citrate, tributyl citrate, and triacetin, although it is possible that other water-insoluble plasticizers (such as acetylated monoglycerides, phthalate esters, castor oil, etc.) may be used. Triethyl citrate is an especially preferred plasticizer.

BSPR:
In addition to the above ingredients, a sustained-release carrier may also include suitable quantities of pharmaceutical adjuvants, e.g., diluents, lubricants, binders, granulating aids, colorants, flavorants and glidants that are conventional in the pharmaceutical art. A non-limiting list of suitable adjuvants include spray dried lactose, polyvinylpyrrolidone (PVP), talc, magnesium stearate, and mixtures thereof. The quantities of these additional materials will be sufficient to provide the desired effect to the desired formulation. The sustained-release carrier may contain up to about 50% by weight of pharmaceutical adjuvant(s).

BSPR:
The sustained-release profile of the matrix formulations of the invention can be altered, for example, by varying the amount of retardant, e.g., hydrophobic polymer, by varying the amount of plasticizer relative to hydrophobic polymer, by the inclusion of additional ingredients or excipients, by altering the method of manufacture, etc.

BSPR:
The sustained-release matrix according to the invention provides sustained-release of the active agent for a period of, e.g. about 8 to about 24 hours or more.

BSPR:
Sustained-release carrier formulations, e.g., matrix formulations, may be prepared in accordance with the present invention using any art-known techniques. The sustained-release carrier formulations may be prepared, e.g., melt-granulation, wet granulation, melt-extrusion, dry blending, wet-extrusion, or by other art-known techniques.

BSPR:
In preferred embodiments of the invention, the sustained-release matrix is prepared by wet-granulating the requisite amounts of sustained-release carrier and augmented microcrystalline cellulose to form a moistened mass. Preferably, the sustained-release carrier and augmented microcrystalline cellulose are in powder form. The moistened mass is then screened and dried, e.g. using a fluid bed dryer. The dried granulate may then be further screened to obtain a

granulate within a desired uniform particle size. The dried granulate may then be divided into unit doses and encapsulated in a hard gelatin capsule, or compressed into tablets of desired size and shape.

BSPR:
In other embodiments, a pre-manufactured sustained-release matrix is prepared to which the active agent is added. The mixture is then wet-granulated as described above, and, e.g. compressed to form a tablet. For example, a sustained-release matrix may be prepared by blending a mixture of xanthan gum, locust bean gum and an augmented microcrystalline cellulose in powder form in a granulator, e.g., a high speed mixer. A sufficient amount of water is added to the mixture, which is fater blended. The mixed product, which is now in the form of a wet mass, is removed from the granulator and dried, e.g. in a fluid bed dryer. The dried granulation is screened to produce dried granules within a desired particle size range. The sustained-release excipient is then ready to be used as a sustained release matrix which is suitable for direct compression with any active medicament to form a sustained-release dosage form. Alternatively, the dried screened granules may be encapsulated in hard gelatin capsules to produce the final solid sustained-release dosage form.

BSPR:
Additional pharmaceutical processing aids such as lubricants, e.g. magnesium stearate may be added to the sustained-release carrier or sustained-release excipient prior to further processing.

BSPR:
The active agent may be wet-granulated together with the sustained-release carrier and/or augmented microcrystalline cellulose. The resultant moistened mass is then processed as described above to obtain the desired final dosage form.

BSPR:
In a preferred embodiment, the active agent is added to the augmented microcrystalline cellulose during manufacture of the excipient proper. Then, the requisite amount of augmented microcrystalline cellulose/active agent blend is combined with the sustained-release carrier and further processed to produce the final dosage form.

BSPR:
The sustained-release coating includes at least one sustained-release carrier, such as described hereinabove. In embodiments of the invention including a sustained-release coating, the immediate release core comprising the augmented microcrystalline cellulose and the active ingredient is coated with a sufficient amount of sustained-release coating to provide sustained-release of the active ingredient, e.g. for up to about 8 to about 24 hours. The amount of sustained-release coating applied to the core is typically in the range of, e.g. a weight gain level from about 2 to about 30 percent, although the overcoat may be greater depending upon the physical properties of the particular active agent utilized and the desired release rate, and other factors known to those skilled in the art.

BSPR:
The sustained-release coating is preferably an aqueous or organic based coating. Preferably, the sustained-release coating includes a hydrophobic or hydrophilic material.

BSPR:
In certain preferred embodiments of the present invention, the sustained-release coating includes a hydrophobic polymer, e.g. a pharmaceutically acceptable acrylic polymer, including but not limited to acrylic acid and methacrylic acid copolymers, methyl methacrylate copolymers, ethoxyethyl methacrylates, cynaoethyl methacrylate, aminoalkyl methacrylate copolymer, poly(acrylic acid), poly(methacrylic acid), methacrylic acid alkylamide copolymer, poly(methyl methacrylate), polymethacrylate, polyacrylamide, aminoalkyl methacrylate copolymer, poly(methacrylic acid anhydride), glycidyl methacrylate copolymers,

waxes, fatty acids, shellac, wax-type substances including hydrogentaed castor oil and hydrogenated vegetable oil, synthetic waxes, hydrogenated fats, stearic acid and stearyl alcohol. Examples of suitable commercially available polymethacrylates include Eudragit RS or RL, commercially available from Rohm Tech, Inc.

BSPR:
In other preferred embodiments, the sustained-release coating includes a hydrophobic polymer which is a hydrophobic cellulosic material such as ethylcellulose. Those skilled in the art will appreciate that other cellulosic polymers, including other alkyl cellulosic polymers, may be substituted for part or all of the ethylcellulose included in the hydrophobic polymer coatings of the present invention.

BSPR:
In most preferred embodiments, the sustained release coating is in the form of an aqueous dispersion. One commercially-available aqueous dispersion of ethylcellulose is Aquacoat.RTM. (FMC Corp., Philadelphia, Pa., U.S.A.). Another aqueous dispersion of ethylcellulose is commercially available as Surelease.RTM. (Colorcon, Inc., West Point, Pa., U.S.A.).

BSPR:
In embodiments of the present invention where the sustained-release coating comprises an aqueous dispersion of a hydrophobic polymer, the inclusion of an effective amount of a plasticizer in the aqueous dispersion of hydrophobic polymer will further improve the physical properties of the film. Generally, the amount of plasticizer included in a coating solution is based on the concentration of the hydrophobic polymer, e.g., most often from about 1 to about 50 percent by weight of the hydrophobic polymer. Concentration of the plasticizer, however, can only be properly determined after careful experimentation with the particular coating solution and method of application.

BSPR:
The sustained-release profile of the sustained-release formulations of the invention can be altered, for example, by varying the thickness of the sustained-release coating, changing the particular sustained release carrier used, or altering the relative amounts of, e.g., different acrylic resin lacquers, altering the manner in which the plasticizer is added (e.g., when the sustained-release coating is derived from an aqueous dispersion of hydrophobic polymer), by varying the amount of plasticizer relative to hydrophobic polymer, by the inclusion of additional ingredients or excipients, by altering the method of manufacture, etc.

BSPR:
In other embodiments of the present invention, the sustained-release coating includes an enteric coating material in addition to or instead or the hydrophobic polymer coating. Examples of suitable enteric polymers include cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, polyvinylacetate phthalate, methacrylic acid copolymer, shellac, hydroxypropylmethylcellulose succinate, cellulose acetate trimellitate, and mixtures of any of the foregoing. An example of a suitable commercially available enteric material is available under the trade name Eudragit.TM. L 100-55.

BSPR:
The sustained release or additional coatings may be applied in any pharmaceutically acceptable manner known to those skilled in the art. For example, in one embodiment, the coating is applied via a fluidized bed or in a coating pan. For example, the coated tablets may be dried, e.g., at about 60.degree.-70.degree. C. for about 3-4 hours in a coating pan. The solvent for the sustained-release coating may be organic, aqueous, or a mixture of an organic and an aqueous solvent. The organic solvents may be, e.g., isopropyl alcohol, ethanol, and the like, with or without water.

BSPR:

Any art-known technique may be used to prepare the sustained-release coated dosage forms of the present invention. In one preferred embodiment, simply by way of example, the requisite amounts of active agent and the augmented microcrystalline cellulose are wet granulated to form a moistened mass. The moistened mass is then screened and dried. The dried mass is then compressed to form an immediate release core of desired size and shape, e.g. a tablet.

BSPR:
The immediate release core comprising the active agent and the augmented microcrystalline cellulose is then coated with a sustained-release carrier using any art-known coating process. The resulting sustained-release dosage form may then be dried, e.g. in a fluid bed dryer, if needed.

BSPR:
In preferred embodiments, multiple layers of sustained-release coating may be applied.

BSPR:
Additional coating layers may be applied to the dosage form. Such additional coating layers may be applied prior to or after the application of the sustained-release coating layer(s) as desired. Such additional coating or multiple coating layers may be applied to the immediate release core prior to addition of a sustained-release coat or, alternatively, after coating with the sustained-release coating. Such coating or coatings serve as, e.g. protective and/or barrier functions.

BSPR:
In preferred embodiments of the invention, the ratio of active agent to sustained-release carrier is from about 1:3 to about 1:7 by weight. In other preferred embodiments, the active agent comprises from about 1 to about 80% by weight of the final formulation.

BSPR:
The sustained-release formulations of the invention may also include other pharmaceutical adjuvants, e.g., flavorants, sweeteners and taste masking agents. Generally any flavoring or food additive such as those described in Chemicals Used in Food Processing, pub 1274 by the National Academy of Sciences, pages 63-258 may be used. Generally, the final product may include from about 0.1% to about 5% by weight flavorant.

BSPR:
The sustained-release formulations of the present invention may also contain effective amounts of coloring agents, (e.g., titanium dioxide, F.D. & C. and D. & C. dyes; see the Kirk-Othmer Encyclopedia of Chemical Technology, Vol. 5, pp. 857-884, hereby incorporated by reference), stabilizers, binders, odor controlling agents, and preservatives.

BSPC:
SUSTAINED-RELEASE CARRIER

BSPC:
SUSTAINED-RELEASE COATING FORMULATIONS

DEPR:
A controlled release excipient according to the present invention is prepared as follows. First, 630 g of the augmented microcrystalline cellulose excipient of Example 1 and 270 g of a hydrophilic material comprising 135 g of xanthan gum and 135 g of locust bean gum, all in a powder form having an average particle size of less than 50 microns are blended for two minutes in a granulator (i.e., a high speed mixer having a combination chopper/impeller). After pre-mixing, 100 ml of water is added until there is sharp rise in the power consumption (about 2-3 minutes). The mixed product, which is now in the form of granules, is removed from the granulator and dried in a convection air-oven for 24 hours at a temperature of about 40.degree.-60.degree. C. The dried granulation is then passed through a 20 mesh screen. The product is now ready to be granulated with

an active, the result of which is suitable for compression to form a sustained-release tablet.

DEPR:
Veraparnil HCl is a relatively soluble active ingredient which has a dose of about 240 mg in a sustained-release tablet form. The active ingredient (verapamil) is granulated with the sustained-release carrier as follows. The 385 g of the sustained-release carrier is first blended with 115 g verapamil HCL for two minutes in a granulator. After premixing, about 90 ml of water is added until there is a sharp rise in the power consumed by the granulator (about 2-3 minutes). The mixed product, which is now in the form of granules, is removed from the granulator and dried in a convection air-oven for 24 hours at a temperature of about 40.degree.-60.degree. C. The dried granulation is then passed through a 20 mesh screen. The final composition of the mixture is about 77.0% of the sustained-release carrier and 23.0% of verapamil HCl.

DEPR:
The mixture is blended with hydrogenated vegetable oil for about 5 minutes in a V-blender. Magnesium stearate is then added and the mixture is blended for an additional 4 minutes. The final composition of the mixtures is about 75.0% of the sustained-release carrier, 22.5% verapamil HCl, 2.00% hydrogenated vegetable oil, and 0.500% magnesium stearate, by weight. The mixture is then compressed on a Stokes RB-2 rotary tablet press with sixteen stations. The average weight of the tablets produced is about 1067 mg and the crushing strength about 7-8 kgs. Each tablet contains about 240.08 verapamil, 800.25 mg sustained-release carrier, 21.34 mg hydrogenated vegetable oil, and 5.34 mg magnesium stearate.

DEPR:
A sustained-release verapamil tablet is prepared in accordance with Example 3, except that the augmented microcrystalline cellulose of Example 2 is used. The resultant tablet provided an in-vitro dissolution profile indicative of a sustained-release verapamil formulation.

DEPR:
A sustained-release verapamil tablet is prepared in accordance with Example 5, a 50:50 blend of the excipients of Examples 1 and 2 are used. The resultant tablet produced an in-vitro dissolution profile indicative of a sustained-release verapamil formulation.

DEPR:
A sustained-release carrier according to the present invention is prepared as follows. First 600 g of the excipient of Example 1 and 300 g of a mixture of xanthan gum and locust bean gum in approximately a 1:1 ratio, all in powder form having an average particle size of less than about 50 microns, are blended for two minutes in a granulator (i.e., a high speed mixer having a combination chopper/impeller). About 125 ml of water is added to the mixture until there is a sharp rise in the power consumed (about 2-3 rminutes). The mixed product, which is now in the form of granules, is removed from the granulator and dried in a convection air-oven for 24 hours at a temperature of about 40.degree.-60.degree. C. The dried granulation is then passed through a 20 mesh screen. The product is now ready to be used as a slow release carrier which is suitable for direct compression with any active medicament to form a sustained-release tablet.

DEPR:
Sustained-release tablets according to the present invention are prepared as follows. The sustained-release carrier as prepared above is first blended with chlorpheniramine maleate for 10 minutes in a V-blender. Magnesium stearate is then added as a lubricant and the mixture is blended for an additional 5 minutes. The final composition of the mixture is about 87.5% of the sustained-release carrier, 12% chlorpheniramine maleate, and 0.5% magnesium stearate by weight.

DEPR:
In this example, sustained-release tablets are prepared in accordance with the

procedure set forth in Example 6 above, except that 600 mg of the excipient of Example 2 is used. The resultant tablets produced an in-vitro dissolution profile indicative of a sustained release chlorpheniramine formulation.

DEPR:
In this example, sustained-release tablets are prepared in accordance with the procedure set forth in Example 6 above, except that a combination of 300 mg of the excipient of Example 1 and 300 mg of the excipient of Example 2 is used.

DEPR:
Sustained-release tablets containing 40 mg metoclopramide were prepared with the following ingredients:

DEPR:
The tablets are prepared as follows. The resultant tablets provide sustained-release of metoclopramide. The metoclopramide, 50% of the xanthan gum and the excipient of Example 1 are deaggregated through a 6 mesh screen into a blender and the powders are mixed for approximately 3 minutes at high speed. A solution of polyvinyl pyrrolidone in isopropyl alcohol was prepared and added to the mixing powders over a 30 second period. Further mixing and addition of isopropyl alcohol was carried out to produce suitable granules.

DEPR:
The wet granules mass was discharged through a 4 mesh screen into the drying bowl of a fluid bed dryer. The granules were dried until the moisture level reached below 1% w/w. The dry granules were sieved through a 16 mesh screen, weighed and blended with the remaining portion of the xanthan gum and stearic acid for 30 minutes and compressed on a tablet press to produce sustained release tablets containing 40 mg metoclopromide.

DEPR:
Sustained-release tablets containing 150 mg indomethacin were prepared in the same way as described in Example 9 from the following ingredients:

DEPR:
Sustained-release tablets containing 300 mg theophylline were prepared in the same manner as described in Example 9 from the following ingredients:

DEPR:
The resultant tablets provide sustained release of theophylline.

DEPR:
In examples 12-16, tablets are prepared similar to those in Example 9 except that an equal amount of the excipient of Example 2 is substituted for the excipient of Example 1. The resultant tablets provide sustained-release of the active ingredient.

DEPR:
In examples 19-23, tablets similar to those in Example 9 is prepared except that an equal amount of an excipient comprising microcrystalline cellulose, 0.25% w/w SLS and 5.0% colloidal silicon dioxide is substituted for Excipient 1. The resultant tablets provide sustained release of the active ingredient.

DEPC:
EXAMPLES 3-22--SUSTAINED-RELEASE FORiMULATIONS

CLPR:
2. The method of claim 1, further comprising wet granulating said augmented microcrystalline cellulose and at least a portion of said sustained-release carrier to form a matrix.

CLPR:
5. The method of claim 3, further comprising coating said tablet with a portion of said sustained-release carrier.

CLPR:
7. The method of claim 3, wherein said immediate release core is coated with at least a portion of said sustained-release carrier.

CLPR:
9. The method according to claim 1, further comprising the step of wet granulating said augmented microcrystalline cellulose with said sustained-release carrier.

CLPR:
11. The method according to claim 9, further comprising the step of compressing said active agent, augmented microcrystalline cellulose and said sustained-release carrier into a tablet.

CLPR:
12. The method according to claim 10, further comprising the step of compressing said active agent, augmented microcrystalline cellulose and said sustained-release carrier into a tablet.

CLPR:
13. The method according to claim 11, wherein said sustained-release carrier comprises a retardant selected from the group consisting of alkylcelluloses, acrylic and methacrylic acid polymers and copolymers, polylactides, polyglycolides, cellulose ethers, cellulose esters, polyanhydrides, polyorthoesters, polycaprolactones, polyphosphazenes, polysaccharides, proteinaceous polymers, polypeptides, polyesters, polyorthoesters, hydrophilic polymers, hydrophilic gums, waxes and wax-like materials, and mixtures thereof.

CLPR:
14. The method according to claim 12, wherein said sustained-release carrier comprises a retardant selected from the group consisting of alkylcelluloses, acrylic and methacrylic acid polymers and copolymers, polylactides, polyglycolides, cellulose ethers, cellulose esters, polyanhydrides, polyorthoesters, polycaprolactones, polyphosphazenes, polysaccharides, proteinaceous polymers, polypeptides, polyesters, polyorthoesters, hydrophilic polymers, hydrophilic gums, waxes and wax-like materials, and mixtures thereof.

CLPR:
16. The method according to claim 10, further comprising the steps of compressing said augmented microcrystalline cellulose and said active agent into a tablet and applying said sustained-release carrier as a coating on said tablet.

CLPR:
28. The method of claim 1, wherein said sustained-release carrier comprises a retardant selected from the group consisting of alkylcelluloses, acrylic and methacrylic acid polymers and copolymers, polylactides, polyglycolides, cellulose ethers, cellulose esters, polyanhydrides, polyorthoesters, polycaprolactones, polyphosphazenes, polysaccharides, proteinaceous polymers, polypeptides, polyesters, polyorthoesters, hydrophilic polymers, hydrophilic gums, waxes and wax-like materials, and mixtures thereof.

CLPR:
33. The method of claim 1, further comprising the step of forming a matrix including said augmented microcrystalline cellulose, at least a portion of said sustained release carrier, and said active agent.

CLPR:
35. The method of claim 34, further comprising the step of coating the surface of the tablet with a portion of said sustained-release carrier.

CLPV:
incorporating an effective amount of a sustained-release carrier to obtain a final product which provides sustained-release of said active agent in an environment of use.

L31: Entry 11 of 16 File: USPT Nov 9, 1999

DOCUMENT-IDENTIFIER: US 5980508 A
TITLE: Controlled release device and method

BSPR:
If the sustained release of a single drug dose is desired, the drug is simply mixed with a suitable excipient, loaded into the device and implanted. Whereupon, the action of the body fluids gradually dissolves, disperses or penetrates the excipient and releases the drug over a period of time. If pulsatory delivery is required, the capsule cylinder may be loaded with a succession or `stack` of alternating `active` and `spacer` layers each comprising a suitable excipient, carrier or matrix. Each active layer contains a dose, or a relatively high concentration of the drug(s) to be delivered, while each spacer layer contains no drug(s) or a relatively low concentration thereof. Dissolution, leaching or erosion of each successive layer (by body fluids after implantation) provides the desired pulsatory drug delivery, while the formulation of the excipient of an active layer determines the profile of the corresponding dose, and the formulation of a spacer layer determines the time interval between the doses of the adjacent active layers.

BSPR:
Natural polymers, such as cellulose acetate phthalate, hydroxypropyl cellulose, carboxymethyl cellulose, ethyl cellulose, methyl cellulose, collagen, zein, gelatin, agarose, DEAE, Sephadex T, natural rubber, guar gum, gum agar, curdlan or other schleroglucans, or hydroxymethyl cellulose or albumin are further examples of expanding gels or swelling agents which may be used as driving mechanisms, matrix bases and/or coating excipient material.

DEPR:
Development of systems for single-shot immunisation would eliminate the need for multiple handling of stock, offering particular advantages to livestock industries. Although formulations are available which provide sustained release of antigen, such long exposure may induce antigenic tolerance, highlighting the need for a system which provides pulsatile, rather than continuous release. The use of microsphere combinations of varying size or hardness has recently being trialed in an effort to produce pulsatile antigen release profiles, however maintaining antigen stability has proved difficult and release of each dose generally occurs over an extended period, rather than in discrete, short-lived "pulses". In vitro experiments using the pulsatile antigen delivery device illustrated in FIG. 17 have shown that the "active" doses were released in a discrete pulses, while in vivo trials of prototype devices (FIGS. 18 and 20) have shown that antibody responses were induced to titres equivalent to those of control animals which received tetanus toxoid in a liquid form adjuvanted with aluminium hydroxide gel.

L31: Entry 15 of 16 File: USPT Jul 25, 1989

DOCUMENT-IDENTIFIER: US 4851232 A
TITLE: Drug delivery system with means for obtaining desirable in vivo release rate pattern

DEPR:
In accordance with the practice of the invention, delivery device 10 can be made with a reservoir 12 of a material that does not adversely affect drug 14, an animal or other host. The presently preferred materials useful for forming reservoir 12 comprise hydrogels that exhibit the ability to swell in water and retain a significant fraction of water within its structure. In one embodiment, the hydrogels can be noncross-linked, or in another embodiment they may be cross-linked with an acid mobile covalent or ionic bonds sensitive to slow acidic hydrolysis. The term mobile is used in its standard meaning to denote the bond breaks in an acidic environment. The hydrogels can be selected from the group consisting of plant or animal origin, hydrogels prepared by modifying naturally occurring structures, and synthetic polymeric hydrogels. The polymeric hydrogels swell or expand to a very high degree, usually exhibiting a 2 to 50 fold volume increase. Hydrophilic polymeric materials useful for the purpose include poly(hydroxyalkyl methacrylate); poly(electrolyte complexes); poly(vinyl acetate) cross-linked with hydrolyzable bonds; waterswellable N-vinyl lactams; polysaccharides; natural gum; agar; agrose; sodium alginate; carrageenan; fucoidan; furcellaran; laminaran, hypnea; eucheuma; gum arabic; gum ghatti; gum karaya; gum tragacanth; locust beam gun; chitosan; arbinoglactan; pectin; amylopectin; gelatin; hydrophilic colloids such as carboxymethyl cellulose gum or alginate gum crossed-linked with a polyol such as propylene glycol; and the like, cellulose ethers comprising hydroxypropylmethylcellulose exhibiting a viscosity of from 3 to 260,000 centipoises, a degree of polymerization of from 40 to 2100, and a molecular weight having a number average of from 9,200 to 350,000; and hydroxypropylcellulose ether having a hydroxypropyl content of 7 to 16%.

DEPR:
In another example, a delivery device is made by first preparing sustained release tiny pills by blending 400 ml of ethyl cellulosewater, 70:30% solution, 7.5% w:v, with 375 g of theophylline, 150 g of mannitol and 475 g of magnesium stearate and the blend kneaded and passed through an extrusion granulation machine. After drying at 115.degree.-120.degree. F., the cores are passed through a 20 mesh screen and coated with a wall of ethyl cellulose in an air suspension machine to yield tiny timed pills. Next, a multiplicity of tiny pills are blended with a hydrogel reservoir forming polymer consisting essentially of a coherent meshwork that imbibes and immobilizes water, powdered alginate gugm crossed-linked with propylene glycol, and the mixture is compressed in a tablet machine using 11/32 inch deep concave punch to yield the drug delivery device for orally administering as a bronchodilator in the management of status asthmaticus, and as a pulmonary vasodilator and smooth muscle relaxant. Other forms of theophylline can be used in the subject delivery device such as theophylline sodium acetate, theophylline sodium glycinate, {7-(2,3-dihydroxypropyl)] theophylline, theophylline meglumine and theophylline monoethanolamine.

CLPV:
(a) a matrix shaped and sized for oral admittance into the environment of use, the matrix comprising a pharmaceutically acceptable non-toxic hydroxypropylcellulose that absorbs fluid from the gastrointestinal tract,

expands and exhibits a 2 to 50 fold volume increase and comprises a hydroxypropyl content of 7 to 16%; and,

CLPV:
(a) a matrix adapted for oral admittance into the gastrointestinal tract, the matrix comprising a pharmaceutically acceptable nontoxic hydroxypropylcellulose that absorbs fluid from the gastrointestinal tract, retains some fluid within its matrix structure, expands from 2 to 50 fold volume increase and comprises a hydroxypropyl content of 7 to 16%; and,

L31: Entry 7 of 16 File: USPT Sep 26, 2000

DOCUMENT-IDENTIFIER: US 6124355 A
TITLE: Oxybutynin therapy

BSPR:
In light of the above presentation it will be appreciated by those versed in the medical and pharmaceutical dispensing arts to which this invention pertains that a pressing need exists for a dosage form and for a therapeutic composition that can deliver the valuable drug oxybutynin in a controlled, extended dose to a patient in clinical need of incontinence management. The pressing need exits for an oral dosage form, for a therapeutic composition and for a method of therapy that can deliver oxybutynin at a controlled rate in a substantially constant dose per unit time for its beneficial therapeutic effect. The need exists further for a dosage form and a therapeutic composition that can deliver oxybutynin protected from light to insure that a complete dose of oxybutynin is administered to the patient and still remains substantially independent of the changing environment of the gastrointestinal tract. The need exists additionally for a sustained-release dosage form comprising the therapeutic composition that can deliver a therapeutic dose of oxybutynin for its intended effect, for avoiding an overdose, and for lessening the side effects that can accompany the drug. It will be appreciated further by those skilled in the dispensing art that if such a novel and unique dosage form, therapeutic composition and method are made available that can administer oxybutynin in a beneficial dose over time and simultaneously provide oxybutynin while lessening the incidence of both over and under dose, the dosage form, the therapeutic composition, and their accompanying methods would represent an advancement and a valuable contribution to the medical arts.

BSPR:
Another object of the present invention is to provide a sustained-release dosage form for orally administering oxybutynin in a controlled dose for the nonsurgical treatment of incontinence in a human afflicted with incontinence.

BSPR:
Another object of the invention is to provide a method of administering oxybutynin in a sustained-release profile to lessen side effects.

DEPR:
The invention provides a dosage form for the delivery of the therapeutic composition comprising oxybutynin. The dosage form comprises a wall, which wall surrounds an internal lumen or compartment. The wall comprises a semipermeable composition that is permeable to the passage of fluid and impermeable to the passage of oxybutynin. The wall is nontoxic and it comprises a polymer selected from the group consisting of a cellulose acylate, cellulose diacylate, cellulose triacylate, cellulose acetate, cellulose diacetate and cellulose triacetate. The wall comprises 75 wt % (weight percent) to 100 wt % of the cellulosic wall-forming polymer; or, the wall can comprise additionally 0.01 wt % to 10 wt % of polyethylene glycol, or 1 wt % to 25 wt % of a cellulose, either selected from the group consisting of hydroxypropylcellulose or hydroxypropylalkycellulose such as hydroxypropylmethylcellulose. The total weight percent of all components comprising the wall is equal to 100 wt %. The internal compartment comprises the therapeutic oxybutynin composition in layered position with an expandable hydrogel composition. The expandable hydrogel composition in the compartment increases in dimension by imbibing the fluid

through the semipermeable wall, causing the hydrogel to imbibe the fluid, expand and occupy space in the compartment, whereby the drug composition is pushed from the dosage form. The therapeutic layer and the expandable layer act together during the operation of the dosage form for the release of oxybutynin to a patient over time. The dosage form comprises a passageway in the wall that connects the exterior of the dosage form with the internal compartment. The dosage form provided by the invention delivers oxybutynin from the dosage form to the patient at a zero order rate of release over a period of 24 hours.

CLPR:
1. A sustained-release oxybutynin formulation for oral administration to a patient comprising a therapeutic dose of an oxybutynin selected from the group consisting of oxybutynin and its pharmaceutically acceptable salt that delivers from 0 to 20% of the oxybutynin in 0 to 4 hours, from 20 to 50% of the oxybutynin in 0 to 8 hours, from 50 to 85% of the oxybutynin in 0 to 14 hours, and greater than 75% of the oxybutynin in 0 to 24 hours for treating incontinence in the patient.

CLPR:
2. A sustained-release oxybutynin formulation for oral administration to a patient in need of treatment for urge incontinence comprising a therapeutic dose of an oxybutynin selected from the group consisting of oxybutynin and its pharmaceutically acceptable salt that delivers from 0 to 1 mg in 0 to 4 hours, from 1 mg to 2.5 mg in 0 to 8 hours, from 2.75 to 4.25 mg in 0 to 14 hours, and 3.75 mg to 5 mg in 0 to 24 hours for treating urge incontinence in the patient.

CLPR:
3. A sustained-release oxybutynin solid dosage form for oral administration to a patient for treating incontinence comprising an oxybutynin selected from the group consisting of oxybutynin and its pharmaceutically acceptable salt that administers up to 2 mg of the member in 0 to 4 hours, from 2 mg to 5 mg of the member in 0 to 8 hours, from 5 mg to 8.5 mg of the member in 0 to 14 hours, and greater than 7.5 mg in 0 to 24 hours for treating incontinence in the patient.

CLPR:
4. A sustained-release oxybutynin dosage form for oral administration to a patient for treating incontinence comprising an oxybutynin selected from the group consisting of oxybutynin and its pharmaceutically acceptable salt that administers up to 3 mg in 0 to 4 hours, 3 mg to 7.5 mg in 0 to 8 hours, 8 mg to 13 mg in 0 to 14 hours, and 12 mg to 15 mg in 0 to 24 hours for treating incontinence in the patient.

CLPR:
5. A dosage form for the oral administration of oxybutynin to a patient for treating incontinence, wherein the dosage form comprises a therapeutic dose of oxybutynin that is administered in a sustained-release cumulative dose of 0.2% to 80% over 2 to 16 hours.

CLPR:
8. A dosage form for the oral administration of oxybutynin to a patient for treating incontinence, wherein the dosage form comprises a therapeutic dose of oxybutynin that is administered in a sustained release rate of 0.5% to 7% per hour over 30 minutes to 22 hours.

CLPR:
16. A method for treating incontinence in a patient, wherein the method comprises administering orally to the patient a dosage form comprising a therapeutic dose of oxybutynin that is administered in a sustained-release cumulative dose of 0.2% to 80% over 2 to 16 hours for treating incontinence.

CLPR:
19. A method for treating incontinence in a patient, wherein the method comprises administering orally to the patient a dosage form comprising a therapeutic dose of oxybutynin that is administered in a sustained release rate of 0.5% to 7% per hour over 30 minutes to 22 hours for treating incontinence.

DB Name	Query	Hit Count	Set Name
USPT	l26 and l24	2	L27
USPT	dioctyl sodium sulfosuccinate or dss or stool softener	3385	L26
USPT	l1 and l24	0	L25
USPT	expand$4 same l10	63	L24
USPT	expand$4 same polymer	10237	L23
USPT	l5 and l10	0	L22
USPT	l5 same l10	0	L21
USPT	l5 same polymer	0	L20
USPT	l5 and polymer$1	1	L19
USPT	l15 same l16	3078	L18
USPT	l16.ti. l16.ab.	0	L17
USPT	block$4 or obstruct$4	1002487	L16
USPT	swell$4	60392	L15
USPT	l12 and l13	13	L14
USPT	sustained release	12822	L13
USPT	l1 and l10	38	L12
USPT	l5 and l10	0	L11
USPT	hydroxyethylcellulose or hydroxy ethyl cellulose or hydroxyethyl cellulose	20946	L10
USPT	l1 and l2	0	L9
USPT	l1 and l7	0	L8
USPT	l2.ti. or l2.ab.	10	L7
USPT	l5 and l2	0	L6
USPT	l1.ti. or l1.ab.	1	L5
USPT	l1 near l2	0	L4
USPT	l1 same l2	0	L3
USPT	(fed or postprandial or digestive) near1 mode	471	L2
USPT	docusate	173	L1

L24: Entry 53 of 63 File: USPT May 10, 1983

DOCUMENT-IDENTIFIER: US 4382999 A
TITLE: Water-swellable composite caulking material for preventing water leakage

BSPR:
There are known several rubbery compositions compounded with particles of a water-absorbing polymeric material, such as a polyvinyl alcohol, polymer of an acrylic acid salt, carboxymethylcellulose, hydroxyethylcellulose and the like, dispersed in the matrix of a rubber (see, for example, Japanese Pat. Kokai No. 53-143653, 54-7461, 54-7463 and 54-20066) which are capable of expanding when swollen with water and useful as a caulking material for preventing water leakage. These compositions have several problems as a caulking material that the swelling pressure as one of the most important characteristics for the caulking effect cannot be sufficiently high because of the relatively low swelling ratio of the material due to the solubility of the dispersed phase of the water-absorbing material in water and that the velocity of water absorption is low so that no instant caulking effect can be obtained with the composition. Further, there is also known a rubbery composition in which the water-absorbing dispersed material is a urethane polymer. The swelling pressure obtained with a caulking material of this type is also relatively low due to the insufficient affinity of the urethane polymer to water in addition to the problem of the extremely low velocity of water absorption.

L24: Entry 3 of 63 File: USPT Jan 16, 2001

DOCUMENT-IDENTIFIER: US 6174547 B1
TITLE: Dosage form comprising liquid formulation

DEPR:
Capsule 15, distant from orifice 13, contains an expandable composition 18, initially in contact with the end of capsule 15. Expandable composition 18 is a push-driving force that acts in cooperation with dosage form 10 and capsule 15 for delivering a drug 20 emulsion formulation 19 from dosage 10. Composition 18 exhibits fluid imbibing and/or absorbing properties. Composition 18 comprises a hydrophilic polymer that can interact with water and aqueous biological fluids and then swell or expand. The hydrophilic polymers are known also as osmopolymers, osmogels, and hydrogels, and they exhibit a concentration gradient across wall 12, whereby they imbibe fluid into dosage form 10. Representative of hydrophilic polymers are poly(alkylene oxide) of 1,000,000 to 10,000,000 weight average molecular weight including poly(ethylene oxide), and an alkali carboxymethylcellulose of 10,000 to 6,000,000 weight average molecular weight including sodium carboxymethylcellulose. Composition 18 may comprise 10 mg to 425 mg of osmopolymer. Composition 18 comprises 1 to 50 mg of a poly(cellulose) of a member selected from the group consisting of hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, and hydroxypropylbutylcellulose. Composition 18 comprises 0.5 mg to 75 mg of an osmotically effective solute, known also as osmotic solute and osmagent, that imbibe fluid through wall 12 into dosage form 10. The osmotically effective solutes are selected from the group consisting of a salt, acid, amine, ester and carbohydrate selected from the group consisting of magnesium sulfate, magnesium chloride, potassium sulfate, sodium sulfate, lithium sulfate, potassium acid phosphate, mannitol, urea, inositol, magnesium succinate, tartaric acid, sodium chloride, potassium chloride, and carbohydrates such as raffinose, sucrose, glucose, lactose, and sorbitol. Composition 18 optionally comprise 0 wt % to 3.5 wt % of a colorant, such as ferric oxide. The total weight of all components in composition 18 is equal to 100 wt %.

L24: Entry 2 of 63 File: USPT Feb 6, 2001

DOCUMENT-IDENTIFIER: US 6183466 B1
TITLE: Dosage form comprising a capsule

DEPR:
Dosage form 10 houses an expandable composition 19 distant from mouth 15 and initially separate and in contact with end 20 of capsule 16. Composition 19 is a driving force that acts in cooperation with dosage form 10 and capsule 16 for delivering a drug formulation from dosage form 10. Composition 19 exhibits fluid absorbing and/or fluid imbibing properties. Composition 19 comprises a hydrophilic polymer that can interact with water and aqueous biological fluids imbibed into dosage form 10 and then swell or expand. The hydrophilic polymers 21 are known also as osmopolymers, hydrogels and osmogels as they exhibit a concentration gradient across wall 12, and thereby absorb or imbibe fluid into dosage form 10. Representative of osmopolymers 21 are poly(ethylene oxide) having a 750,000 to 10,000,000 weight average molecular weight, and, an alkali carboxymethylcellulose of 10,000 to 6,000,000 weight average molecular weight such as sodium carboxymethylcellulose. Composition 19 comprises 10 mg to 475 mg of hydrophilic polymer 21. Composition 19 can comprise additionally 1 mg to 75 mg of poly(cellulose) 22, a member selected from the group consisting of hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, and hydroxypropylbutylcellulose. Driving force composition 19 comprises 0.5 mg to 175 mg of an osmotically effective solute 23, known also as osmagents, that imbibe fluid through wall 12 into dosage form 10. The osmotically effective solutes are selected from the group consisting of salt, acid, amine, ester and carbohydrate as represented by a member selected from the group consisting of magnesium sulfate, magnesium chloride, potassium sulfate, sodium sulfate, lithium sulfate, potassium acid phosphate, mannitol, urea, inositol, magnesium succinate, tartaric acid, sodium chloride, potassium chloride, and carbohydrates such as raffinose, sucrose, glucose, lactose, and sorbitol. Composition 19 optionally comprises 0 wt % to 3.5 wt % of a colorant such as ferric oxide. The total weight of all components in composition 19 is equal to 100 wt %.

L24: Entry 8 of 63 File: USPT Sep 19, 2000

DOCUMENT-IDENTIFIER: US 6120803 A
TITLE: Prolonged release active agent dosage form adapted for gastric retention

DEPR:
The present invention is described and characterized by one or more of the following technical features and/or characteristics, either alone or in combination with one or more of the other features and characteristics: an active agent dosage form adapted for gastric retention that comprises (a) a therapeutically-effective amount of an active agent, (b) a polymer matrix in which the active agent is dissolved or dispersed, the polymer matrix including a high molecular weight, water-soluble polymer and a hydroattractant, preferably water insoluble, the polymer matrix having an outer surface for exposure to the environment of use, (c) a band of insoluble material circumscribing a portion of the surface of the polymer matrix, and optionally a gastric-emptying delaying agent; a number average molecular weight of the water-soluble polymer being between about 100,000 and 20,000,000 grams per mole; the water soluble polymer being polyethylene oxide, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, hydroxyethyl cellulose, sodium carboxy methylcellulose, calcium carboxymethyl cellulose, methyl cellulose, pre-gelatinized starch, maltodextrin, polyacrylic acid or its sodium or potassium salts, or polyvinyl alcohol; the hydroattractant being low-substituted hydroxypropyl cellulose, microcrystalline cellulose, cross-linked sodium or calcium carboxymethyl cellulose, cellulose fiber, cross-linked polyvinyl pyrrolidone, cross-linked Amberlite resin, alginates, colloidal magnesium-aluminum silicate, cross-linked polyacrylic acid or its sodium or potassium salts, corn starch granules, rice starch granules, potato starch granules, or sodium carboxymethyl starch; a gastric retentive dosage form adapted for delivery of active agents that are relatively insoluble or have a short absorption window in the small intestine, such as where the active agent is an antiviral, antimicrobial or antifungal active agent, and especially where the active agent is acyclovir, ganciclovir, cimetidine, ranitidine, captopril, methyldopa, selegiline, minocycline or fexofenadine or a pharmaceutically acceptable salt thereof; a polymer matrix in which the weight percent of the water soluble polymer in the polymer matrix is about 10 to 90 weight percent and weight percent of the hydroattractant in the polymer matrix is about 5 to 70 weight percent; a dosage form adapted to deliver in the stomach, as a single dose and over a prolonged time period, preferably at least 4 hours, and even more preferably 8-12 hours, a therapeutically-effective amount of an active agent, with the relative absorption index of the dosage form being at least 0.5, and preferably at least 1.0; a unitary compressed dispersion of a solid active agent in a gel-forming, erodible polymer matrix having a first portion that swells in the stomach while maintaining its physical integrity for a prolonged period of time and a second, non-erodible, non-gel-forming portion for promoting retention of the dosage form in the stomach over a prolonged period of time; the water soluble polymer being polyethylene oxide having a number average molecular weight of at least 100,000 grams per mole; a composition comprising about 5 weight percent to about 50 weight percent of a polyethylene oxide polymer having a number average molecular weight of between about 100,000 and 20,000,000 grams per mole and about 5 weight percent to about 60 weight percent of a hydroxypropyl cellulose polymer having a hydroxypropyl content of between about 10 weight percent and about 13 weight percent of the hydroxypropyl cellulose polymer; an active agent dosage form adapted for gastric retention comprising an active agent selected from the group consisting of acyclovir, ganciclovir, metformin, bupropion, orlistat and minocycline, and a

bioerodible polymer, wherein the dosage form releases a therapeutically effective amount of the active agent to the stomach of a subject over at least a 6 hour period; an active agent dosage form adapted for gastric retention comprising an active agent reservoir adapted to deliver active agent over a prolonged period to the stomach of a subject to which the dosage form is administered and a polymer matrix including a high molecular weight, water-soluble polymer and a hydroattractant combined with the active agent reservoir and adapted to expand when contacted with fluid in the stomach of the subject and promote retention of the dosage form in the stomach of the subject; a dosage form wherein the polymer matrix is tubular and surrounds the active agent reservoir comprising a band of insoluble material circumscribing at least a portion of the polymer matrix; delivery of active agent from the active agent reservoir that is osmotically driven; gastric-retentive, bioerodible active agent dosage forms adapted to deliver an active agent at a controlled rate such that the relative absorption index of the active agent delivered is at least 0.5; a gastric-retentive, bioerodible active agent dosage form adapted to deliver a therapeutically effective amount of the active agents acyclovir, ganciclovir, cimetidine, ranitidine, captropil, methyldopa, selegiline, minocycline, metformin, bupropion, orlistat and fexofenadine, or a pharmaceutically acceptable salt thereof, to the stomach of a subject over a sustained retention period and bioequivalents thereof; a method of treating a subject in need thereof with an active agent that comprises administering the active agent to the subject in an active agent dosage form comprising a water soluble, swellable polymer and a hydroattractant adapted for gastric retention and release of the active agent over a prolonged period; a dosage form and method for administering at least 500 mg of acyclovir to a subject over at least a 12 hour period ; a dosage form and method for administering at least 500 mg of ganciclovir to a subject over at least a 12 hour period; a dosage form and method for administering at least 100 mg of minocycline to a patient over at least a 12 hour period; a method of administering a gastric retentive dosage form that is adapted to swell in the stomach of a subject that comprises administering the dosage form to the subject in the fed state.

WEST

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L14: Entry 10 of 13 File: USPT Aug 12, 1997

DOCUMENT-IDENTIFIER: US 5656290 A
TITLE: Bisacodyl dosage form with multiple enteric polymer coatings for colonic delivery

BSPR:
Colonic delivery dosage forms are known in the art. For example, U.S. Pat. No. 5,171,580, issued Dec. 15, 1992, Boehringer Ingelheim Italia, teaches a preparation for delivery in the large intestine and especially the colon, comprising an active containing core coated with three protection layers of coatings having different solubilities. The inner layer is Eudragit.RTM.S, with a coating thickness of about 40-120 microns, the intermediate coating layer is a swellable polymer with a coating thickness of about 40-120 microns, and the outer layer is cellulose acetate phthalate, hydroxypropylmethyl cellulose phthalate, polyvinyl acetate phthalate, hydroxyethyl cellulose phthalate, cellulose acetate tetrahydrophthalate, or Eudragit.RTM.L. In the dosage forms of the present invention Eudragit.RTM.S is only used as an outer layer.

BSPR:
The dosage forms of the present invention are to be distinguished from controlled (sustained) release compositions which slowly release a drug active over an extended period of time and extend the duration of drug action over that achieved with conventional delivery. The dosage forms of the present invention prevent the release of the drug active until the dosage form reaches the colon.

BSPR:
The micronized bisacodyl, inclusion complex of bisacodyl and a cyclodextrin, solid dispersion of bisacodyl on a hydrophilic substrate, and commercially available bisacodyl powder may be admixed with various other solid pharmaceutically acceptable excipients to enhance the dissolution rate of bisacodyl by promoting disintegration into primary drug particles to maximize surface area. Acceptable excipients include, but are not limited to, diluents (e.g., lactose, sucrose, glucose, starch, calcium sulfate, dicalcium phosphate, micro crystalline cellulose); binders (e.g., polyvinylpyrrolidone, pregelatinized starch, gelatin, hydroxypropyl methylcellulose, methylcellulose, hydroxyethyl cellulose, hydroxypropyl cellulose); lubricants (e.g., stearic acid, magnesium stearate); disintegrants (e.g., sodium starch glycolate, cross-linked polyvinylpyrrolidone, cross-linked carboxymethyl cellulose); gildants (e.g., fumed silica); and buffers. Pharmaceutical excipients are disclosed in "Remington's Pharmaceutical Sciences", 17th Ed. (1985), pp. 1603-1644, which is herein incorporated by reference. The solids mixture may be prepared via a number of techniques well-known in the pharmaceutical sciences such as dry mixing, wet granulation, and fluid bed granulation, and be coated on the surface of, or incorporated into a spherical substrate, elliptical substrate, or incorporated into a hard capsule or compressed tablet, using conventional equipment and processes.

BSPR:
The compositions of the present inventions can optionally include active drug ingredients in addition to bisacodyl. Non-limiting examples of other active drug agents and amounts typically present in such compositions include the following: docusate sodium, calcium or potassium, from about 5 mg to about 500 mg, preferably from about 50 mg to about 250 mg; glycyrrhiza extract comprising from about 5% to about 30%, preferably from about 10% to about 16%, glycyrrhizic acid, from about 2 mg to about 200 mg, preferably from about 20 mg to about 100

mg; aloe, from about 50 mg to about 500 mg, preferably from about 195 mg to about 325 mg; peppermint oil, from about 250 mg to about 4000 mg, preferably from about 500 mg to about 2500 mg; poloxamer 188, from about 10 mg to about 500 mg, preferably from about 100 mg to about 250 mg; ginger, from about 650 mg to about 1300 mg; mineral oil, USP, from about 500 mg to about 40 g; preferably from about 800 mg to about 20 g; castor oil, USP, from about 500 mg to about 60 g; preferably from about 1 g to about 45 g; and magnesium hydroxide, from about 500 mg to about 5 g, preferably from about 1 g to about 2.8 g.

L12: Entry 1 of 38 File: USPT Jun 19, 2001

DOCUMENT-IDENTIFIER: US 6248363 B1
TITLE: Solid carriers for improved delivery of active ingredients in pharmaceutical compositions

DEPR:
The hydrophilic surfactant can also be, or include as a component, an ionic surfactant. Preferred ionic surfactants include alkyl ammonium salts; bile acids and salts, analogues, and derivatives thereof; fusidic acid and derivatives thereof; fatty acid derivatives of amino acids, oligopeptides, and polypeptides; glyceride derivatives of amino acids, oligopeptides, and polypeptides; acyl lactylates; mono-,diacetylated tartaric acid esters of mono-,diglycerides; succinylated monoglycerides; citric acid esters of mono-,diglycerides; alginate salts; propylene glycol alginate; lecithins and hydrogenated lecithins; lysolecithin and hydrogenated lysolecithins; lysophospholipids and derivatives thereof; phospholipids and derivatives thereof; salts of alkylsulfates; salts of fatty acids; sodium docusate; camitines; and mixtures thereof.

DEPR:
More preferable ionic surfactants include bile acids and salts, analogues, and derivatives thereof; lecithins, lysolecithin, phospholipids, lysophospholipids and derivatives thereof; salts of alkylsulfates; salts of fatty acids; sodium docusate; acyl lactylates; mono-,diacetylated tartaric acid esters of mono-,diglycerides; succinylated monoglycerides; citric acid esters of mono-,diglycerides; carnitines; and mixtures thereof.

DEPR:
More specifically, preferred ionic surfactants are lecithin, lysolecithin, phosphatidylcholine, phosphatidylethanolamine, phosphatidylglycerol, phosphatidic acid, phosphatidylserine, lysophosphatidylcholine, lysophosphatidylethanolamine, lysophosphatidylglycerol, lysophosphatidic acid, lysophosphatidylserine, PEG-phosphatidylethanolamine, PVP-phosphatidylethanolamine, lactylic esters of fatty acids, stearoyl-2-lactylate, stearoyl lactylate, succinylated monoglycerides, mono/diacetylated tartaric acid esters of mono/diglycerides, citric acid esters of mono/diglycerides, cholate, taurocholate, glycocholate, deoxycholate, taurodeoxycholate, chenodeoxycholate, glycodeoxycholate, glycochenodeoxycholate, taurochenodeoxycholate, ursodeoxycholate, tauroursodeoxycholate, glycoursodeoxycholate, cholylsarcosine, N-methyl taurocholate, caproate, caprylate, caprate, laurate, myristate, palmitate, oleate, ricinoleate, linoleate, linolenate, stearate, lauryl sulfate, teracecyl sulfate, docusate, lauroyl carnitines, palmitoyl carnitines, myristoyl camitines, and salts and mixtures thereof.

DEPR:
Particularly preferred ionic surfactants are lecithin, lysolecithin, phosphatidylcholine, phosphatidylethanolamine, phosphatidylglycerol, lysophosphatidylcholine, PEG-phosphatidylethanolamine, lactylic esters of fatty acids, stearoyl-2-lactylate, stearoyl lactylate, succinylated monoglycerides, mono/diacetylated tartaric acid esters of mono/diglycerides, citric acid esters of mono/diglycerides, cholate, taurocholate, glycocholate, deoxycholate, taurodeoxycholate, glycodeoxycholate, cholylsarcosine, caproate, caprylate, caprate, laurate, oleate, lauryl sulfate, docusate, and salts and mixtures thereof, with the most preferred ionic surfactants being lecithin, lactylic

esters of fatty acids, stearoyl-2-lactylate, stearoyl lactylate, succinylated monoglycerides, mono/diacetylated tartaric acid esters of mono/diglycerides, citric acid esters of mono/diglycerides, taurocholate, caprylate, caprate, oleate, lauryl sulfate, docusate, and salts and mixtures thereof.

DEPR:
Extended release coating: The term "extended release coating" as used herein means a coating designed to effect delivery over an extended period of time. Preferably, the extended release coating is a pH-independent coating formed of, for example, ethyl cellulose, hydroxypropyl cellulose, methylcellulose, hydroxymethyl cellulose, hydroxyethyl cellulose, acrylic esters, or sodium carboxymethyl cellulose. Various extended release dosage forms can be readily designed by one skilled in art to achieve delivery to both the small and large intestines, to only the small intestine, or to only the large intestine, depending upon the choice of coating materials and/or coating thickness.

DETL:
TABLE 18 Ionic Surfactants COMPOUND HLB FATTY ACID SALTS >10 Sodium caproate Sodium caprylate Sodium caprate Sodium laurate Sodium mynstate Sodium myristolate Sodium palmitate Sodium palmitoleate Sodium oleate 18 Sodium ricinoleate Sodium linoleate Sodium linolenate Sodium stearate Sodium lauryl sulfate (dodecyl) 40 Sodium tetradecyl sulfate Sodium lauryl sarcosinate Sodium dioctyl sulfosuccinate [sodium docusate (Cytec)] BILE SALTS >10 Sodium cholate Sodium taurocholate Sodium glycocholate Sodium deoxycholate Sodium taurodeoxycholate Sodium glycodeoxycholate Sodium ursodeoxycholate Sodium chenodeoxycholate Sodium taurochenodeoxycholate Sodium glyco cheno deoxycholate Sodium cholylsarcosinate Sodium N-methyl taurocholate Sodium lithocholate PHOSPHOLIPIDS Egg/Soy lecithin [Epikuron .TM. (Lucas Meyer), Ovothin .TM. (Lucas Meyer)] Lyso egg/soy lecithin Hydroxylated lecithin Lysophosphatidylcholine Cardiolipin Sphingomyelin Phosphatidyichoiine Phosphatidyl effianolamine Phosphatidic acid Phosphatidyl glycerol Phosphatidyl serine PHOSPHORIC ACID ESTERS Diethanolammonium polyoxyethylene-10 oleyl ether phosphate Esterification products of fatty alcohols or fatty alcohol ethoxylates with phosphoric acid or anhydride CARBOXYLATES Ether carboxylates (by oxidation of terminal OH group of fatty alcohol ethoxylates) Succinylated monoglycerides [LAMEGIN ZE (Henkel)] Sodium stearyl filmarate Stearoyl propylene glycol hydrogen succinate Mono/diacetylated tartaric acid esters of mono- and diglycerides Citric acid esters of mono-, diglycerides Glyceryl-lacto esters of fatty acids (CFR ref. 172.352) Acyl lactylates: lactylic esters of fatty acids calcium/sodium stearoyl-2-lactylate calcium/sodium stearoyl lactylate Alginate salts Propylene glycol alginate SULFATES AND SULFONATES Ethoxylated alkyl sulfates Alkyl benzene sulfones .alpha.-olefin sulfonates Acyl isethionates Acyl taurates Alkyl glyceryl ether sulfonates Octyl sulfosuccinate disodium Disodium undecylenamideo-MEA-sulfosuccinate CATIONIC Surfactants >10 Lauroyl carnitine Palmitoyl carnitine Myristoyl carnitine Hexadecyl triammonium bromide Decyl trimethyl ammonium bromide Cetyl trimethyl ammonium bromide Dodecyl ammonium chloride Alkyl benzyldimethylammonium salts Diisobutyl phenoxyethoxydimethyl benzylammonium salts Alkylpyridinium salts Betaines (trialkylglycine): Lauryl betaine (N-lauryl,N,N-dimethylglycine) Ethoxylated amines: Polyoxyethylene-15 coconut amine

CLPR:
18. The pharmaceutical composition of claim 17, wherein the ionic surfactant is selected from the group consisting of alkyl ammonium salts; bile acids and salts, analogues, and derivatives thereof; fatty acid derivatives of amino acids, carnitines, oligopeptides, and polypeptides; glyceride derivatives of amino acids, oligopeptides, and polypeptides; acyl lactylates; mono-,diacetylated tartaric acid esters of mono-,diglycerides; succinylated monoglycerides; citric acid esters of mono-,diglycerides; alginate salts; propylene glycol alginate; lecithins and hydrogenated lecithins; lysolecithin and hydrogenated lysolecithins; lysophospholipids and derivatives thereof; phospholipids and derivatives thereof; salts of alkylsulfates; salts of fatty acids; sodium docusate; and mixtures thereof.

CLPR:

44. The pharmaceutical composition of claim 43, wherein the ionic surfactant is selected from the group consisting of alkyl ammonium salts; bile acids and salts, analogues, and derivatives thereof; fatty acid derivatives of amino acids, carnitines, oligopeptides, and polypeptides; glyceride derivatives of amino acids, oligopeptides, and polypeptides; acyl lactylates; mono-,diacetylated tartaric acid esters of mono-,diglycerides; succinylated monoglycerides; citric acid esters of mono-,diglycerides; alginate salts; propylene glycol alginate; lecithins and hydrogenated lecithins; lysolecithin and hydrogenated lysolecithins; lysophospholipids and derivatives thereof; phospholipids and derivatives thereof; salts of alkylsulfates; salts of fatty acids; sodium docusate; and mixtures thereof.